Scientific consensus – "Addiction":
Smoking is a repetitive behavior mediated by many factors.

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Summary

After extensive review of published literature we conclude that no universally accepted scientific definition for the term addiction exists, limiting its usefulness as the basis for scientific research. Cigarette smoking is a complex, highly interactive behavior involving psychosocial, sensory, and pharmacological elements as many of the researchers in this field have suggested. Smoker exposure to cigarette smoke is determined by some of the following behaviors, e.g. the choice to smoke or not to smoke, selection of the brand, and smoking topography, i.e. how they smoke it. Given that our ultimate goal is to give insights into the key question of the relationships between smoking behavior, smoker exposure, and potentially "reduced harm" products, we believe that it can best be achieved when approaching it as such, i.e. as a complex behavior, rather than from the perspective of the much over-used and often misapplied term of addiction.

In order to attain this goal, we conclude that each of the above components of smoking behavior should be studied individually but understood collectively. A portion of these has been addressed in our internal investigations as seen in the projects in 2001, and also is reflected in the external investigations as seen in the accepted research proposals to our External Research Program. Gap analysis, based on the results of these projects, will provide future focus for research.

I. Objectives of the project

The objectives of the project are to clarify

1) current scientific understanding of addiction among PM scientists
2) how nicotine and smoking behavior fit into this understanding
3) the extent to which nicotine and/or other smoke constituents influence smoker exposure
4) the behavioral parameters that influence smoker exposure, and
5) how to integrate the above and thereby contribute to our harm reduction efforts

The participants and their scientific background by training are as follows (in an alphabetical order of the family name):

Carchman, Richard: pharmacology
Davies, Bruce: molecular pharmacology/biochemistry
Gullotta, Frank: experimental/physiological psychology (until November 2001)
Ritter, Mitchel: clinical psychology (until December 2001)
Roethig, Hans-Juergen: clinical pharmacology (from March 2001)
Takada, Kohji: behavioral pharmacology
Tricker, Anthony: chemistry (from January 2001)

The "team" was formed originally in March 2000. This manuscript represents current understanding on this issue by the team as of November 2001.

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II. Current understanding of the concept of "addiction"

Our initial efforts (March, 2000) at generating a single scientific definition of addiction proved extremely difficult, as what was suggested reflected perspectives from the different disciplines of the participants. Not surprisingly, this also reflected the diversity of the literature on addiction.[1] This mutual educational process resulted in the realization that a pluri-disciplinary approach offered a far richer path towards understanding what is essentially a multidimensional question.

After reviewing the literature[2] from many perspectives including nicotine pharmacology, behavioral pharmacology, sensory physiology, substances of use and abuse, clinical perspectives, sociological and situational factors, and genetic susceptibility, we conclude that no universally accepted scientific definition for the term addiction exists, limiting its usefulness as the basis for scientific research. This is not only our internal thoughts since the same conclusion on the definition of the term has been derived by leading scientists in the field of psychopharmacology:

"Despite the wide-ranging and authoritative 1988 review by the US Surgeon General, views questioning the addictiveness of nicotine continue to be expressed in some quarters. This lack of complete consensus is not unexpected, since no universally agreed scientific definition of addiction exists."[3]

The PM website in October 2000 states that "we agree with the overwhelming medical and scientific consensus that cigarette smoking is addictive"[4] We concur with this position, to the extent how this term is most commonly used today.[5] However, the statement does not

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[1] For definitions by public health authorities see Appendix A. As for changes in definition as seen in a leading pharmacological textbook see Appendix B.

[2] Literature reviewed through June 2001 including scientific books and publications, governmental and non-governmental reports, textbooks and company research. Major events are listed chronologically in Appendix G. References for the entire document are listed in Appendix H.

[3] Stolerman IP, Jarvis, MJ, The scientific case that nicotine is addictive, Psychopharmacol 117: 2-10 (1995)

[4]URL: http://www.philipmorris.com (October 2000)
As for various definitions in various languages and chronological changes of the definition of the term as nonscientific usage, see Appendix C. As for the evolution/history of PM position on the term addiction and the "position" of nicotine and/or smoking, see Appendix D.

[5]Current usage of the term by non-scientists appears to connote the following:

A repetitive behavior suggesting a "loss of control", which may have a positive (e.g. "health food" addict) or a negative ("junk food" addict) outcome.

Public Health Authorities appear to use the term to connote:

A repetitive behavior associated with an adverse health outcome, suggesting a "loss of control" attributable to some inherent characteristic or property of the substance and/or behavior.

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provide insight into the key question of the relationships between smoking behavior and exposure.

- We achieved consensus in a number of areas that we believe would be informative and thereby enable us to develop and implement harm reduction strategies. As part of this consensus, we adopted, as an operating principle, **not only to approach these areas individually, but also to understand them collectively.**

Based on the above operating principle, areas to be covered would include:

- CNS pharmacology – modulation of nicotinic acetylcholine receptors
- Peripheral pharmacology – cardiovascular effects, sensory aspects (modulation of afferent nerves)
- Psychological aspects – repetitive behavior and affect management
- Sociological aspects – social interactions and situational factors
- Developmental aspects – changes from initiation to cessation and relapse

III. Addiction or smoking behavior as a determinant of exposure? – our working model

Regarding "addiction" or "addictive behaviors", the following descriptions in the field of clinical psychology[6] would be relevant to depict the broad spectrum of the issue:

- "Drug abuse and addiction have been considered the consequence of a complicated blend of biological, psychological and sociological factors. In short, drug abuse and addiction reside neither in the drug nor in the personality of the user."

- "Addictive behaviors are the result of any interactive factors that vary in prominence from individual to individual. It is essential to take a multidimensional view of drug use, abuse and addiction; the psychological determinants of drug use, the developmental phase in which abuse occurs, the social and cultural contexts in which toxicants are used and abused, and the pharmacological properties of the substance."

In order to capture the spectrum that is involved in smoking behavior *per se*, the following description in the field of psychiatry/psychopharmacology[7] would be relevant:

> "Despite decades of research into motives for tobacco smoking, the question of why people smoke is still a challenge. The critical role of nicotine dependence has recently been acknowledged *[reference omitted]*. However, it is also clear that the interactions

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(agreement of the team in August, 2000, that still holds as of July 2001)

[6] Shaffer, H.J. and Jones, S.B., *Quitting Cocaine: The Struggle Against Impulse*, Lexington Books, pp. 37-77, 1989

[7] Fagerstrom, K.O., Schneider, N.G., Measuring nicotine dependence: a review of the Fagerstrom tolerance questionnaire, J Behav Med 12: 159-182 (1989)

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among the psychosocial, sensory, and pharmacologic reinforcing mechanisms are complex *[reference omitted]* and their relative roles unknown."

Our operating principle for approaching smoking behavior[8] as the determinant of exposure is as follows:

- As the above quotations summarize, our consensus defines/considers addiction as a complex, highly interactive behavior which must be considered in light of those interactions rather than from a purely reductionist perspective. When considering smoking, it is for this reason that smoking behavior becomes the more appropriate term rather than the term addiction. With respect to exposure and in view of our position that smoking behavior is the determinant of exposure, a careful study applying our operating principles appears to be the most promising approach towards developing, and contributing to the harm reduction program.

- These include:
  - Smoking involves very complex psychological and social behaviors
  - Nicotine is a centrally as well as a peripherally active compound
  - The pharmacological effects of nicotine are important, but are probably not the sole determinant of smoking behavior, and
  - Recent scientific findings suggest other tobacco smoke constituents acting by themselves or by potentially modulating the effects of nicotine, may possess central and/or peripheral effects relevant to smoking behavior and therefore exposure.

- Therefore, a successful approach is based on the analysis of individual components of smoking behavior coupled with a collective understanding. In addition to the areas to cover described above, necessary data may also be obtainable from the following topics:
  - Cessation programs, e.g. pharmacotherapy, behavior modification
  - Multi-substance use: patterns of behavior, substitution (physical dependence)
  - Substance-prone personality
  - Factors determining "chippers"
  - Other substance-related behaviors, e.g. role of the alleviation of withdrawal signs

IV. Smoking behavior as the overall determinant to exposure

Smoker exposure is determined by some of the following behaviors, e.g. the choice to smoke or not to smoke, selection of the brand, and smoking topography.

Individual components of smoking behavior (including smoking topography) can be covered by the following areas:

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[8]see Chap IV.

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- Pharmacology
- Psychology
- Sociology
- Developmental aspects

These comprise the individual components that define smoking behavior operationally. Our understanding of smoking behavior, as it relates to exposure, requires their integration if we are going to succeed in achieving significant harm reduction. Indeed, that nicotine is not the sole determinant of smoking behavior has been recognized for over a decade: ".. that cigarette smoking, like other forms of drug abuse, is critically but only partially mediated by pharmacologic factors;..."[9]. Possible outcomes of the examination through these components are as follows:

Pharmacological components

Current scientific thinking suggests that nicotine plays a significant role in smoking behavior, and therefore exposure to smoke constituents.[10] It is not known whether other active components of tobacco smoke exist in a form which would also influence smoking behavior. It is therefore of considerable importance, in terms of harm reduction, to characterize as precisely and completely as possible, the effect of nicotine on smoking behavior, to identify other potential smoke constituents, and to understand their differential effects. Once we have a more complete understanding of the factors involved, the following can be considered:

- Possible reformulation of our products that might modify the effects of smoke constituents on smoking behavior
- Develop theoretical and ultimately experimental models, reflecting the complex interactions between active compounds in tobacco smoke and smoking behavior, further contributing to reducing smoker exposure

Psychological components

Many researchers involved in the fields of psychology regarding substance use and abuse suggest that the origins of this behavior lie in the psychological dynamics[11] of the user. This may involve aspects of repetitive behavior, affect management, coping strategies, stress reduction, and cognitive enhancement.

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[9] Henningfield, J.E., Pharmacologic basis and treatment of cigarette smoking, J Clin Psychiat 45: 24-34 (1984)

[10] Public health authorities appear to support the notion that nicotine determines smoking behavior. For example, conclusions of the US Surgeon General's Report 1988 include: "After carefully examining the available evidence, this Report concludes that:

- Cigarette and other forms of tobacco are addicting.
- Nicotine is the drug in tobacco that causes addition..."

Further, one of the three precepts of a report by the US Institute of Medicine (2001) is: "nicotine is addictive."

[11] Pharmacological effects may contribute to this dynamic.

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Understanding the conditions under which tobacco products are consumed, should provide us with a better understanding of how exposure is determined by the consumers themselves, first independently of the pharmacological properties of tobacco products, their effects and potential, and then in conjunction, in light of our interactive model. Internal discussion on the topograhic changes in smoking behavior when smokers switch from one brand to another has been conducted elsewhere.[12]

In short, by elucidating the psychological factors involved in the use of tobacco products may provide insights into their consumption, thereby contributing to a long-term harm reduction.

Sociological components

Smoking behavior, particularly as it relates to initiation – though not excluding other moments in the smoking career - is greatly influenced by the context surrounding it. Factors such as family, peer group, socio-economic level, social activities all may play significant roles in the development of smoking behavior, and therefore smoker exposure.

Though difficult to reduce to specific mechanisms, understanding the interactions between tobacco products, their perception and use in society as a whole, as well as in specific sub-groups, will enhance our ability to perceive the phenomenon in all its complexity. Further, it may allow us to propose and execute means towards better prevention of smoking by minors and enabling smokers to make decisions about a risky product intended for use by an adult population.

Developmental aspects

Current scientific thinking suggests that specific periods of life constitute moments when the potential for substance use is higher than others. Smoking can be seen as a developmental process (rather than a static state) where the subject passes through different phases, from experimentation, initiation into "confirmation" and maintenance, and possibly culminating in cessation. Each phase is under the influence of various other factors including those in other components described above. For example, dose or exposure level may play a critical role in this process; however, determining factors for each transition as they relate to the specific periods of life have yet to be elucidated. A better understanding of these factors may enable us to reduce their effects during critical periods.

V. What do we know about nicotine as it relates to smoking behavior?

As has been mentioned above, public health authorities appear to think that nicotine solely

[12] See the discussion by the "consensus – compensation" group.

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determines smoking behavior. This section summarizes current knowledge on this aspect,[13] which is one of the objectives of this project, i.e. to clarify the extent to which nicotine determines smoker exposure. This can be rephrased into "to what extent nicotine controls such smoking behaviors."

Pharmacodynamics

Reinforcing effects of nicotine

Positively reinforcing effects of intravenous nicotine have been reported in various species of animals and in humans; but the general consensus appears to be that the reinforcing efficacy of nicotine is relatively weak (see Appendix E). Aversive effects of intravenous nicotine have also been reported in monkeys and in humans at the same dose level required for positive reinforcement.[14] These make the determination of the role of nicotine in controlling smoking behavior difficult. Based on our reading of the available data, we believe that though important, nicotine probably is not the sole determinant of smoker exposure, at least for the population at large.

Putative biochemical changes in the brain involved in nicotine reward

Dopamine: The stimulation of the mesolimbic dopaminergic system has been considered to play a crucial role in mediating the drug reward. In rodents, nicotine has been reported to increase the extracellular level of dopamine in this brain region, and this is often interpreted as evidence for the "addictiveness" of nicotine, since similar phenomena have been observed with prototypic drugs of abuse such as cocaine and morphine. However, whether or not a similar change in the midbrain dopaminergic system is induced by nicotine in nonhuman primates and man is not clear. For example, Dr. Domino, a leading scientist in the field of nicotine pharmacology, states based on his "preliminary data" that, "[i]t appears that nicotine releases very little dopamine in monkey brains, contrary to its effect in rats."[15] Further, reports which cast doubt on this theory are appearing based on the facts that an increase in midbrain dopamine levels is also observable after aversive stimuli such as electric shocks and stressful events have been given.[16] Recent thinking is that midbrain dopamine would serve more "as an 'error' or 'learning' signal than as a mediator of hedonic experience."[17]

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[13] See Appendix E for more detailed description. For a published review, see e.g. Frenk, H. and Dar, R., *A Critique of Nicotine Dependence*, Kluwer Academic Pub., 2000.

[14] e.g. "Clearly, the data are not consistent with descriptions of nicotine as consistently serving as a positive reinforcer or an aversive stimulus, or simply as a toxin lacking behavioral effects. Nicotine appears to be a particularly malleable stimulus." (Henningfield, J.E., Goldberg, S.R., Control of behavior by intravenous nicotine injections in human subjects, Pharmacol Biochem Behav 19:1021-1026, 1983)

[15] Domino, personal communication (2000).

[16] e.g. Salamone, J.D., Cousins, M.S., Snyder, B.J., Behavioral functions of nucleus accumbens dopamine: empirical and conceptural problems with the anhedonia hypothesis, Neurosci Biobehav Rev 21: 341-359 (1997)

[17] e.g. Hyman, S.E., Malenka, R.C., Addiction and the brain: the neurobiology of compulsion and its persistence, Nature Rev Neurosci 2: 695-703 (2001)

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Neuronal nicotinic acetylcholine receptors (nAChR): Configuration of nAChRs, their distribution in the brain, and their functions are being studied vigorously. However, despite the accumulation of a significant body of knowledge, much remains to be elucidated. Recently it has been reported that the α7 nicotinic receptor is involved in the rewarding effects of nicotine such that methyllcaconitine (MLA), an α7 receptor antagonist, attenuated the effects of nicotine and cocaine in the intracranial self-stimulation paradigm in rats.[18] In addition, the elevation in the α7 receptor mRNA level has been reported in some brain areas after chronic nicotine treatment.[19] Whether or not, or how these reflect the rewarding and other functional effects of nicotine remains to be studied, in addition to the functional roles of various nAChR subtypes in the human brain.

Other neurotransmission systems: Involvement of other neurotransmission systems has also been suggested. For example, intra-ventral tegmental area injection of muscimol or baclofen, GABAa and GABAb agonists, respectively, has been reported to suppress intravenous self-administration of nicotine in rats.[20] Involvement of NMDA-type glutamatergic receptors has also been suggested in mediating the rewarding effects of opioids.[21] Whether or not the same is true for nicotine remains to be elucidated.

In summary, much remains to be studied on the precise brain mechanism(s) underlying the reinforcing effects of nicotine.

Withdrawal signs after chronic nicotine treatment and smoking cessation

Although some withdrawal signs have been reported after chronic treatment of nicotine in rodents, a general agreement among researchers appears to be that the detection of nicotine withdrawal signs in rodents is difficult. Further in rhesus monkeys, "no observable withdrawal signs are developed following hourly intravenous administration of nicotine in a dose of 0.25 mg/kg/injection for 4 weeks."[22]. These data appear to indicate that the physical dependence potential of nicotine is weak in nature. In humans, various signs have been reported to be observed upon cessation of smoking

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[18] Panagis, G., Kastellakis A., Spyraki C., Nomikos, G., Effects of methyllycaconitine (MLA), and α7 nicotinic receptor antagonist, on nicotine- and cocaine-induced potentiation of brain stimulation reward, Psychopharmacol 149: 388-396 (2000)

[19] Ryan, R.E., Loiacono, R.E., Nicotine regulates alpha7 nicotinic receptor subunit mRNA: implications for nicotine dependence, Neuroreport 12: 569-572 (2001)

[20] Corrigall, W. A., Coen, K. M., Adamson, K. L., Chow, B. L., Zhang, J., Response of nicotine self-administration in the rat to manipulations of mu-opioid and gamma-aminobutyric acid receptors in the ventral tegmental area, Psychopharmacol 149: 107-14(2000)

[21] Narita, M., Aoki, T., Suzuki, T., Molecular evidence for the involvement of NR2B subunit containing N-methyl-D-aspartate receptors in the development of morphine-induce place preference, Neurosci 101: 601-606 (2000)

[22] Domino, E.F., Round table on nicotinic receptors in addiction: summary report, Eur J Pharmacol 393: 315-320 (2000)

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and disease criteria have been established both in ICD-10 by WHO[23] and DSM-IV by APA[24] (see Appendix F). However, it has been reported that de-nicotinized cigarettes also alleviated withdrawal signs in humans.[25] Thus, it appears that to what extent the withdrawal signs observable upon smoking cessation are pharmacologically mediated requires further studies.

Pharmacological intervention of smoking behavior

Seemingly based on the notion that smoking is nicotine-taking, and that it is difficult for smokers to quit smoking due to the development of physical dependence on nicotine, various pharmacological "aids" for cessation of the behavior have been studied. Among these, the US Public Health Service lists sustained-release bupropion HCl (an antidepressant with adrenergic and dopaminergic agonistic activities), nicotine gum, nicotine inhalor, nicotine nasal spray, and nicotine patch as the 5 first-line pharmacotherapies for tobacco dependence.[26] The 2nd-line pharmacotherapies listed are clonidine (an α-1 adrenergic agonist) and nortriptiline (an adrenergic agonist). Pharmacotherapy utilizing pure nicotine is generally classified as "Nicotine Replacement Therapy" (NRT), and the efficacy of NRT so far has not been reported to be robust: the highest one-year abstinence rate by NRT was 29%, with the lowest being 9%.[27] Blockade of nicotinic acetylcholine receptors by the antagonist mecamylamine appears to increase incidence of smoking; however, mecamylamine did not precipitate withdrawal symptoms.[28] These data appear to support our notion that though important, nicotine is not the sole determinant of smoking behavior.

Other proposed pharmacological tools include the 5HT1A antagonist LY426965, antitussive dextromethorphan, and the CYP2A6 inhibitor methoxsalen, but these are still at the preclinical phase except for methoxsalen (see below).

Effect on cognition, memory and "mood"

It has been well documented that nicotine affects cognition and memory both in animals and humans (see reviews[29]). It has also been reported that smoking is

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[23] The World Health Organization, The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines, 1992.

[24] American Psychiatric Association, Diagnostics and Statistical Manual of Mental Disorders DSM-IV, 1994.

[25] e.g., Butschkey, M.F., Bailey, D., Henningfield, J.E., Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers, Pharmacol Biochem Behav 50: 91-96 (1995)

[26] Fiore, M.C. et al., A clinical practice guideline for treating tobacco use and dependence – a US Publich Healther Service Report, JAMA 283: 3244-3254 (2000)

[27] Richmond, R.L., A comparison of measures used to assess effectiveness of the transdermal nicotine patch at 1 year, Addict Behav 22: 753-757 (1997)

[28] Eissenberg T., Griffiths, R.R., Stitzer, M.L., Mecamylamine does not precipitate withdrawal in cigarette smokers, Psychopharmacol 127: 328-336 (1996)

[29] e.g. Levin, E.D., Simon, B.R., Nicotinic acetylcholine involvement in cognitive function in animals, Psychopharmacol 138: 217-230 (1998)

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effective in improving cognitive performance.[30] To what extent nicotine plays a role, however, is yet to be determined in the latter case.

"Mood"

It is difficult to isolate mood-altering effect from the effects described above, but it is well known that many smokers perceive smoking as "relaxing".[31] Although several studies in animals have reported anxiolytic effects following nicotine injections, the effects were not robust and some studies could not detect the anxiolytic effects of nicotine. Thus, the mood-altering effect of smoking does not appear to be solely explainable by nicotine.

Pharmacokinetics

Nicotine is considered to be initially metabolized by CYP2A6 in the liver, and it has been reported that people with deficient enzyme activity smoke less, due to reduced nicotine metabolism.[32] Recently, however, the method used in these studies has been criticized to give erroneous genotyping. Indeed, recent reports indicate that CYP2A6 gene polymorphism shows "no significant effect on smoking behavior", at least in the populations tested.[33] Yet it has also been reported that methoxsalen, a CYP2A6 inhibitor, decreases smoking.[34]

Peripheral effects – sensory stimulation

- Both cigarette smoking and peripheral administration of nicotine stimulates the sensory branches of five of the twelve cranial nerves:[35] in the mouth, the chorda tympani, glossopharyngeal and trigeminal nerves; in the throat, the glossopharyngeal and vagus nerves; and in the nose, the olfactory and trigeminal nerves. Given the fact that smoking and nicotine stimulate so many nerves it should not be surprising that both smoking and nicotine have pronounced flavor properties.

- One line of evidence suggests that sensory factors play an important role in the regulation of smoke intake[36] as observed in the effect of de-nicotinized cigarette on

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[30] e.g. Parkin, C. et al., The effects of cigarette smoking on overnight performance, Psychopharmacology 136: 172-178 (1998)

[31] Dunn, W.L., *Smoking Behavior: Motives and Incentives*, Washington, D.C., V.H. Winston, pp. xi (1973)

[32] e.g. Pianezza, M.L., Sellers, E.M., Tyndale, R.F., Nicotine metabolism defect reduces smoking, Nature 393: 750 (1998)

[33] e.g. Zhang, X. et al., Lack of association between smoking and CYP2A6 gene polymorphisms in a Japanese population, JPN J. Alcohol & Drug Dependence 36: 486-490 (2001)

[34] Sellers, E.M., Kaplan, H.L., Tyndale R.F., Inhibition of cytochrome P450A6 increases nicotine's oral bioavailability and decreases smoking, Clin Pharmacol Exp Ther 68: 35-43 (2000)

[35] e.g. see Warwick, R., Williams, P.L., Saunders, W.B., *Gray's Anatomy: 35th British edition*, Philadelphia, pp. 1017-1021 (1973)

[36] e.g. Rose, J.E., Hehm, F.M., Levin, E.D., Role of nicotine dose and sensory cues in the regulation of smoke intake, Pharmacol Biochem Behav 44: 891-900 (1993)

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withdrawal signs. However, the relative contributions of pharmacology and sensory physiology to the smoking behavior is currently unknown. The complexity would be depicted based on a recent study[37] in which "[m]ecamylamine attenuated some of the sensory effects of cigarette smoking, particularly the sensation in the windpipe", yet "no effect was detected on smoking satisfaction ratings," and "[t]he present study found no evidence that mecamylamine precipitated craving for cigarettes." An experiment would need to be conducted where a centrally inactive sensory substitute for nicotine was used. Unfortunately, at present such a substitute does not exist.

Genetic predisposition

Smokers' characteristics such as personal traits have long been discussed.[38] "Neuroticism", which is said to include anxiety, depression and irritability, has been postulated to relate with genetic polymorphism of the serotonin transporter gene 5HTTLPR, and several reports indicate that smoking prevalence and difficulty in smoking cessation relate to neuroticism. For example, some studies report a positive correlation of smoking behavior with 5HTTLPR-S genotype.[39] It has postulated that smoking cessation would be most difficult in those with 5HTTLPR-S genotype and with strong neuroticism. Polymorphism of the dopamine transporter gene has also been studied in relation to novelty seeking and smoking, but the results appear to be mixed.[40]

VII. What needs to be done? – future outlook

In order to provide more insights into the key question of the relationships between smoking behavior, exposure, and potentially "reduced harm" products, gap analysis in the components of smoking behavior listed above appears necessary. Some of the "gaps" identified are being pursued in projects planned for 2001, which include:

- ***Fading study***, which is aimed to determine if nicotine/tar ratio of conventional products can be modified to reduce constituent exposure
- ***Nicotine kinetics as an exposure determinant***, which is aimed to determine the contribution of nicotine kinetics on smoking behavior

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[37] Rose, J.E., Behm F.M., Westman, E.C., Acute effects of nicotine and mecamylamine on tobacco withdrawal symptoms, cigarette reward and ad lib smoking, Pharmacol Biochem Behav 68: 187-197 (2001)

[38] Fisher, R.A., Cancer and smoking, Nature 182: 596 (1958)

[39] e.g. Lesch, K.P. et al., Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region, Science 274: 1527-1531 (1996); Lerman, C. et al., Interacting effcts of the serotonin transporter gene and nicotine dependence, Mol Psychiat 5: 189-192 (2000)

[40] e.g. Sabol, S.Z. et al., A genetic association for cigarette smoking behavior, Health Psychology 18: 7-13 (1999); Jorm A.F. et al., Association of smoking and personality with a polymorphism of the dopamine transporter gene: results from a community survey, Am J Med Genet 96: 331-334 (2000)

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- ***Monoamine oxidase inhibitors (MAO-I's) as determinants of exposure***, which is aimed to determine to what extent MAO-I's play a role in smoking behavior
- ***Enhanced sensory response study***, which is aimed to pursue the possibility whether or not an approach based on enhanced sensory response products result in lowered constituent exposure, and
- ***Simplified aerosol deliver study***, which is aimed to determine if delivery of a simplified aerosol can be utilized to answer specific basic research questions involved in smoking behavior

We believe that many other aspects involving the components of smoking behavior have been, and will be, reflected in research proposals submitted to our External Research Program. However, we as a group, do not have detailed information on these projects.

Further, the current team lacks expertise in some of the individual components of smoking behavior namely psychological, sociological, and developmental aspects. These are the areas, which require a detailed gap analysis. In this sense it will be very helpful to have multi-disciplinary workshops on some of the issues with open questions, and the results can be directly fed back to our understanding on factors controlling smoking behavior and exposure.

Finally, because of the rapid developments on understanding of each component of smoking behavior, most notably in pharmacological components, we feel that constant monitoring/analysis of the developments in each field with collective understanding is necessary, in order to cope with various existing and emerging issues as well as to contribute to harm-reduction strategies.

VIII. Conclusions

- Smoking is a lot more than nicotine-taking
- Smoking behavior determines smoker exposure
- Smoking behavior is key to harm reduction
- We should study components of smoking behavior individually but should understand them collectively

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Appendix A. Definitions by public health authorities

A-1. Reports of WHO Expert Committee on Drug Dependence

WHO Expert Committee on Addiction-producing Drugs 7th Report (1957)[*]

Following description is found in a section entitled "*8. Definition of Habit-Forming Drugs*" (pages 9 and 10):

"Reviewing at this time the definitions of addiction-producing and habit-forming drugs ..., the Committee was of the opinion that the time was ripe for emphasizing again the distinction between addiction and habituation (see Annex, page 12). To this end the following definitions were approved: ..."

"Drug addiction is a state of periodic or chronic intoxication produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include:

(1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means
(2) a tendency to increase the dose
(3) a psychic (psychological) and generally a physical dependence on the effects of the drug
(4) detrimental effect on the individual and on society."

"Drug habituation (habit) is a condition resulting from the repeated consumption of a drug. Its characteristics include:

(1) a desire (but not a compulsion) to continue taking the drug for the sense of improved well-being which it engenders;
(2) little or no tendency to increasing the dose;
(3) some degree of psychic dependence on the effect of the drug, but absence of physical dependence and hence of an abstinence syndrome;
(4) detrimental effects, if any, primarily on the individual."

WHO Expert Committee on Addiction-producing Drugs 13th Report (1964)[**]

Following description is found under the title of *""Drug dependence" to replace the terms "drug addiction" and "drug habituation""* (page 9):

- "The Expert Committee sought also to differentiate addiction from habituation and wrote a definition of the latter which, however, failed in practice to make a clear distinction. The definition of addiction gained some acceptance, but confusion in the use of the terms addiction and habituation and misuse of the former continued.

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* World Health Organization, *Expert Committee on Addiction-producing Drugs. Seventh Report.* WHO Technical Report Series 116 (1957)

** World Health Organization, *Expert Committee on Addiction-producing Drugs. Thirteenth Report.* WHO Technical Report Series 273 (1964)

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

....Hence, the use of the term "drug dependence", with a modifying phrase linking it to a particular drug type in order to differentiate one class of drugs from another, has been given most careful consideration."

- "It must be emphasized that drug dependence is a general term selected for its applicability to all types of drug abuse and carries no connotation of the degree of risk to public health or need for a particular type of drug control."

- As for the types of drugs of dependence, the report classifies barbiturates, cocaine, amphetamine, and cannabis.

- "Dependence" is defined as "a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may not be present. A person may be dependent on more than one drug."

Note:

- the definition above was adopted in ICD-10, 1992.
- the name of the committee was thereafter changed to WHO Expert Committee on Drug Dependence.

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

A-2. US Surgeon General's Reports (SGR) 1964 and 1988

SGR, 1964*

"**DISTINCTION BETWEEN** DRUG **ADDICTION** AND DRUG **HABITUATION**

Smokers and users of tobacco in other forms usually develop some degree of dependence upon the practice, some to the point where significant emotional disturbances occur if they are deprived of its use. The evidence indicates this dependence to be psychogenic in origin. In medical and scientific terminology the practice should be labeled *habituation* to distinguish it clearly from *addiction*, since the biological effects of tobacco, like coffee and other caffeine-containing beverages, betel morsel chewing and the like, are not comparable to those produced by morphine, alcohol, barbiturates, and many other potent addicting drugs. In fact, to make this distinction, the World Health Organization Expert Committee on Drugs Liable to Produce Addiction (35) created the following definitions which are accepted throughout the world as the basis for control of potentially dangerous drugs."

<citation of the definitions of addiction and habituation in the WHO Technical Report Series 116, 1957, which is cited in Appendix A-1 follows the above description; bold and italic letters as in the SGR, 1964, Chapter 13, "Characterization of the Tobacco Habit and Beneficial Effects of Tobacco", pp. 350-351>

In the following section of the report entitled "TOBACCO HABIT CHARACTERIZED AS HABITUATION", following descriptions are noted (*ibid.*, pp. 351):

- "Psychogenic dependence is the common denominator of all drug habits and the primary drive which leads to initiation and relapse to chronic drug use or abuse (25). Although pharmacologic drive is necessary it does not need to be a strong one or to produce profound subjective effects in order that habituation to the use of the crude material becomes a pattern of life. Besides tobacco, the use of caffeine in coffee, tea, and cocoa is the best example in the American culture. Another example, the chewing of the betel morsel, exists on a world scale comparable to tobacco and involves several hundred million individuals of both sexes and of all races, classes, and religions ..."

- "Thus, correctly designating the chronic use of tobacco as habituation rather than addiction carries with it no implication that the habit may be broken easily. It does, however, carry an implication concerning the basic nature of the user and this distinction should be a clear one. It is generally accepted among psychiatrists that addiction to potent drugs is based upon serious personality defects from underlying psychologic or psychiatric disorders which may become manifest in other ways if the drugs are removed ..."

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* U.S. Public Health Service, *Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public Health Service.* U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control. PHS Publication No. 1103 (1964; http://www.cdc.gov/tobacco/sgr/sgr_1964/sgr64.htm)

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

In the summary section of this Chapter, it is stated that:

> "...The tobacco habit should be characterized as an *habituation* rather than an *addiction*, in conformity with accepted World Health Organization definitions, since once established there is little tendency to increase the dose; psychic but not physical dependence is developed; and the detrimental effects are primarily on the individual rather than society. No characteristic abstinence syndrome is developed upon withdrawal..." (italics as in the original; *ibid.*, pp. 354)

SGR, 1988**

- "The term "drug addiction" and "drug dependence" are scientifically equivalent: both terms refer to the behavior of repetitively ingesting mood-altering substances by individuals. The term "drug dependence" has been increasingly adopted in the scientific and medical literature as a more technical term, where as the term "drug addiction" continues to be used by NIDA and other organizations when it is important to provide information at a more general level. Throughout this Report, both terms are used and they are used synonymously." (pp. 7)

- "In this Chapter the term "drug dependence" or "drug addiction" refers to self-administration of a psychoactive drug in a manner that demonstrates that the drug controls or strongly influences behavior. In other words, the individual is no longer entirely free to use or not use the substance. Often times, this reduction in the degree to which use is considered "voluntary" is described as "habitual" or "compulsive" drug use." (pp. 248-249)

** U.S. Department of Health and Human Services, *The Health Consequences of Smoking, Nicotine Addiction: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health & Human Services, Centers for Disease Control and Prevention, DHHS Publication No. (CDC) 88-8406 (1988; http://www.cdc.gov/tobacco/sgr_1988.htm)

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

Detailed comparison[41]

Same in Both: *Compulsive use required in both definitions*
Applies to psychoactive substances

Differences between two definitions:

1964	1988
Distinction made between a habit and addiction.	No distinction between a habit and addiction
Tolerance (tendency to increase dose) **required.**	Tolerance may occur but **not** required
Psychic (psychological) and physical dependence (i.e., withdrawal) **required.**	Psychic and physical dependence may occur but **not** required (i.e., not necessary that withdrawal occurs).
Chronic or periodic intoxication **required.**	Frequent intoxication listed as one of the criteria* thus **not** necessary.
Detrimental effects on the individual and society required.	Use despite harmful effects may occur but **not** required.
Criterion of drug-reinforced behavior implied but not specified.	Must have drug-reinforced behavior.
Stereotypic patterns of use not specified.	Stereotypic patterns of use may occur but **not** required.

*"Diagnostic criteria for psychoactive substance dependence" (citation of the DSM-III-R, American Psychiatric Assoc., 1987; pp. 249 of the SGR 1988)

[41] Originally prepared by Gullotta, 1999.

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

*A-3. UK Royal College of Physicians of London 2000**

- "'Addiction' and 'dependence' are terms whose definition has a social as well as a scientific dimension. In principle, they may be distinguished, but in practice such a distinction serves little purpose and the terms are used interchangeably here....Under the current definition, the terms refer to a situation in which a drug or stimulus has unreasonably come to control behavior".

- Earlier and popular view: "addiction refers to a state in which an individual needs to continue to take a drug in order to stave off unpleasant or dangerous withdrawal effects". "..it addresses just one aspect of a wider problem".

- Intoxication: "This feature no longer appears in any official definition because it is apparent that it is neither a necessary nor a sufficient condition..."

- Criteria for addiction given:
  1. A strong desire to take the drug
  2. Substance taken in larger amounts or longer than intended
  3. Difficulty in controlling use
  4. A great deal of time is present in obtaining, using or recovering from effects of substance
  5. A higher priority given to drug use than to other activities and obligations
  6. Continued use despite harmful consequences
  7. Tolerance: absence of nausea, dizziness and other characteristics
  8. Withdrawal

- "...therefore that no single set of criteria can provide a universal framework for the definition of dependence or addiction".

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* Royal College of Physicians of London, *Nicotine Addiction in Britain – A report of the Tobacco Advisory Group of The Royal College of Physicians*, London: Royal College of Physicians of London (2000)

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

A-4. U.S. Institute of Medicine, 2001[*]

No clear definition of the term addiction is given in this report. Although the general usage of the term leaves an impression that it follows the "definition" as described in the SGR 1988, it appears that the IOM considers "the addiction potential of a drug" on a population basis, such that:

"*Assessment of Addiction.* Various measures and methods have been developed to measure dependence on a drug and its abuse or addiction potential (see Table 9-1). These measures and methods are important in examining harm reduction products since addiction to a drug is one of the determining factors associated with its harmful consequences. **The addictive potential of a drug can be determined by examining the number of individuals, within the general population and among those exposed to the drug**, who are regular users of the drug or are considered dependent on a drug, using specific criteria...." (pp. 257; bold emphasis by Takada)

"Table 9-1 Measures of Dependence or Addiction and Abuse Liability

Measures for Dependence or Severity of Dependence

- Daily or regular smoking (cotinine level)
- DSM criteria
- International Diagnostic Code
- Surgeon General's report, 1988
- Fagerstrom Tolerance Questionnaire
- Fagerstrom Nicotine Dependence Test

Methods to Assess for Addiction or Abuse Liability Surveys

- Daily use or dependence among the general population
- Daily use or dependence among those exposed to the drug
- Escalation of drug use
- Relapse rates

Laboratory models

- Psychoactive or subjective effects
- Drug discrimination
- Conditioned place preference
- Drug self-administration
- Withdrawal"

Other related descriptions noted are (bold emphasis by Takada except where indicated):

- "**Precept 2.** Nicotine is addictive." (pp. 5; bold emphasis as in the original)
- "However, despite the morbidity and mortality caused by tobacco and widespread knowledge by adults and adolescents of its adverse health effects, tobacco use

[*] U.S. Institute of Medicine, *Clearing the Smoke – Assessing the Science Base for Tobacco Harm Reduction*, Washington, D.C.: National Academy Press (2001)

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

continues. The biologically active component in tobacco that is primarily responsible for this is nicotine. Nicotine acts on several organs, including the brain. Nicotine is pleasurable to the user, and it is addictive. Thus, many but not all tobacco users find it very difficult to break their addiction and reduce the risk to their health." (pp. 25)

- "There is disagreement among tobacco control experts about the optimal content of nicotine in tobacco products. Whether nicotine addiction is harmful beyond supporting tobacco use and should, therefore, be the target of public health efforts is not a simple question...Nicotine has pleasurable or rewarding effects, in addition to its addictive properties. However, societal views of addictions per se surround the controversy. Retaining nicotine at pleasurable or addictive levels while reducing the more toxic components of tobacco is another strategy for harm reduction..." (pp. 28-29)

- "Where the substance or behavior is addictive or habit-forming, this may generate a long-term increase in the number of users." (pp. 41)

- "Furthermore, **tobacco addiction involves more than a physical addiction to nicotine, but also behavioral and psychological aspects** that also needs to be targeted in exposure reduction as well as cessation." (pp. 118)

- "The FDA's assertion that cigarettes and smokeless tobacco products may be defined as nicotine delivery devices was based on findings that (1) the effects of nicotine are so widely known that it is foreseeable to a reasonable manufacturer that these products will cause addiction and other pharmacological effects and will be used by the consumers for these effects and to sustain the addiction; (2) consumers use tobacco products mainly to sustain addiction, for mood-altering effects, and for weight loss...and (5) as a consequence, consumers keep using cigarettes and smokeless tobacco to sustain their addiction to nicotine (U.S. DHHS, 1995)." (pp. 127)

- "Physical addiction to nicotine is associated with euphoriant and other psychoactive effects, the development of tolerance, and the experience of withdrawal symptoms when the tobacco product is no longer used (U.S. DHHS, 1988)." (pp. 254-255)

- "The number or type of symptoms experienced varies across different drugs of abuse. **The major difference between nicotine and other drugs is the lack of intoxication that results in behavioral and cognitive disruption** (U.S. DHHS, 1988). However, this makes nicotine no less an agent of addiction or dependence than other drugs (Stolerman and Jarvis, 1995)." (pp. 259)

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

Appendix B. Goodman's and Gilman's The Pharmacological Basis of Therapeutics 1975-1996

Note: bold emphasis by Takada.

Summary

Description in Goodman's and Gilman's The Pharmacological Basis of Therapeutics, a representative pharmacology textbook, appears to have been the mixture of the position of WHO Expert Committee on Drug Dependence and that of the US Surgeon General's Reports. For example, Dr. Jaffe described in the 8th Edition that "Addiction is used to connote a severe degree of drug dependence that is an extreme on a continuum of involvement with drug use." (1990). Dr. O'Brien, taking over the chapter in the 9th Edition, appear to have more inclination towards the "disease criteria", i.e., "The term addiction, when used in this chapter, will refer to compulsive drug use, the entire substance dependence syndrome as defined in DSM IV." (1996). Thus it appears that the definition of the term addiction fluctuates even in this representative textbook of pharmacology.

5th ed., 1975 (by Jaffe, J.H.) states the followings:

- "Compulsive Drug use. One of the hazards in the use of drugs to alter mood and feeling is that some individuals eventually behave as *if the effects produced by a drug, or the conditions associated with its use, are necessary to maintain an optimal state of well being*. Such individuals are said to have a *psychological dependence on the drug (habituation)*. The intensity of this dependence may vary from a mild desire to a "craving" or "compulsion" to use the drug. This need or psychological dependence may then give rise to behavior (compulsive drug use) characterized by a preoccupation with the use and procurement of the drug."

- "Compulsive drug use is usually detrimental both to the user and to the society of which he is a part."

- "*Physical dependence* refers to an altered physiological state produced by the repeated administration of a drug, which necessitates the continued administration of the drug to prevent the appearance of a stereotyped syndrome, *the withdrawal or abstinence syndrome*, characteristic for the particular drug."

- "Addiction. It is possible to describe all known patterns of drug use without employing the terms addict or addiction. In many respects this would be advantageous, for the term addiction, like term abuse, has been used in so many ways that it can no longer be employed without further qualification or elaboration. However, since it is not likely that the term will be dropped from the language, it is appropriate to make an effort to delimit its meaning. The definition used here is somewhat arbitrary, and it is not necessarily identical with other definitions of addiction or drug dependence (see Eddy et al., 1965; National Commission, 1973; World Health Organization, 1973). In this chapter, **the term addiction will be used to mean a behavioral pattern of**

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

compulsive drug use, characterized by overwhelming involvement with the use of a drug, the securing of its supply, and a high tendency to relapse after withdrawal. Addiction is thus viewed as an extreme on a continuum of involvement with drug use and refers in a quantitative rather than a qualitative sense to the degree to which drug use pervades the total life activity of the user. In most instances it will not be possible to state with precision at what point compulsive use should be considered addiction. Anyone who is addicted would be considered drug dependent within the WHO definitions, but within the set of definitions used here the term addiction cannot be used interchangeably with physical dependence. **It is possible to be physically dependent on drugs without being addicted and to be addicted without being physically dependent** (see below)." (bold emphasis by Takada)

7th ed., 1985 (by Jaffe, J.H.):

- "The term addiction will be used to mean a behavioral pattern of drug use, characterized by overwhelming involvement with the use of drug (compulsive use), the securing of its supply, and a high tendency to relapse after withdrawal. Addiction is thus viewed as an extreme on a continuum of involvement with drug use and refers in a quantitative rather than a qualitative sense to the degree to which drug use pervades the total life activity of the user **and to the range of circumstances in which drug use controls his behavior**." (bold emphasis by Takada, showing the difference in description from 1975 edition).

8th ed., 1990 (by Jaffe, J.H.)

- "Drug dependence can be defined as a syndrome in which the use of a drug is given a much higher priority than other behaviors that once had higher value. The dependence syndrome is not absolute, but exists in degrees, and its intensity is gauged by the behaviors that are associated with the use of the drug. No sharp line separates drug dependence from nondependent but recurrent drug use. In its extreme form, drug dependence is associated with compulsive drug-using behavior, and it exhibits the characteristics of a chronic relapsing disorder."
- "**Addiction is used to connote a severe degree of drug dependence that is an extreme on a continuum of involvement with drug use**. The term conveys a quantitative rather than a qualitative sense of the degree to which drug use pervades the total life activity of the user and of the range of circumstances in which drug use controls the user's behavior. Anyone who is addicted would be considered drug dependent by the criteria described above. However, the term addiction cannot be used interchangeably with physical dependence as that term is used here. (bold emphasis by Takada)

9th edition, 1996 (by O'Brien, C.P.)

- "Abuse and addiction have been defined and redefined by several organizations over the past 25 years. The reason for these revisions and disagreements is that **abuse and addiction are behavioral syndromes that exist along a continuum from**

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

minimal use to abuse to addictive use. While tolerance and physical dependence are biological phenomena that can be defined precisely in the laboratory and diagnosed accurately in the clinic, there is an arbitrary aspect to the definitions of the overall behavioral syndromes of abuse and addiction. The most influential system of diagnosis for mental disorders is that published by the American Psychiatric Association (DSM IV, 1994). The APA diagnostic system uses the term *substance dependence* instead of *addiction* for the overall behavioral syndrome. Although widely accepted, this terminology can lead to confusion between *physical dependence* and *psychological dependence*. **The term *addiction*, when used in this chapter, will refer to compulsive drug use, the entire substance dependence syndrome as defined in DSM IV.** This should not be confused with physical dependence alone, a common error among physicians. *Addiction* is not used as a pejorative term; in fact, the journal Addiction is one of the oldest scientific journals in this therapeutic area." (bold emphasis by Takada)

- "The APA defines substance dependence (addiction) as a cluster of symptoms indicating that the individual continues use of the substance despite significant substance-related problems. Evidence of tolerance and withdrawal symptoms are included in the list of symptoms, but neither tolerance nor withdrawal is necessary or sufficient for a diagnosis of substance dependence. Substance abuse, a less severe diagnosis, involves a pattern of adverse consequences from repeated drug use that does not meet criteria for substance dependence."

10th edition, 2001 (by O'Brien, C.P.)

- "Abuse and addiction have been defined and redefined by several organizations over the past 25 years. ... **The term *addiction*, when used in this chapter, refers to compulsive drug use, the entire substance dependence syndrome as defined in DSM IV.** This should not be confused with physical dependence alone, a common error among physicians. *Addiction* is not used as a pejorative term **but rather for clarity of communication**; in fact, the journal Addiction is one of the oldest scientific journals in this therapeutic area." (bold emphasis by Takada)

- "The APA defines substance dependence (addiction) as a cluster of symptoms indicating that the individual continues use of the substance despite significant substance-related problems. Evidence of tolerance and withdrawal symptoms are included in the list of symptoms, but neither tolerance nor withdrawal is necessary or sufficient for a diagnosis of substance dependence. Dependence (addiction) requires three or more of the symptoms, while "abuse" can be diagnosed when only one or two symptoms are present."

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

Appendix C. Various definitions seen in dictionaries

C-1. Definitions of addiction in dictionaries of various languages

To summarize the change in non-scientific usage of the word *addiction* (and *addict,* when available) in various countries, definitions seen in the dictionary are listed below. For historic changes of definitions as seen in Webster's Dictionary and the origin of the word, see Appendices C-2 and C-3.

English

Ad·dic·tion Pronunciation: &-'dik-sh&n, a- Function: *noun*
Date: 1599
1 : the quality or state of being addicted <*addiction* to reading>
2 : compulsive need for and use of a habit-forming substance (as heroin, nicotine, or alcohol) characterized by tolerance and by well-defined physiological symptoms upon withdrawal; *broadly* : persistent compulsive use of a substance known by the user to be harmful
(Merriam-Webster Collegiate Dictionary 10th Edition;
http://www.britannica.com/bcom/dictionary/ ; June 22, 2000)

Chinese

Yin: 1) addiction; habitual craving: He's too fond of the cup. 2) strong interest (in a sport or pastime): have a passion for ball games; He's crazy about swordsman fiction.
(Chinese-English Dictionary, Foreign Language Teaching and Research Press, Beijing, 1995)

Yin: 1) originally refers to a habit which is not good, e.g. cigarette smoking, alcohol drinking. 2) also generally refers to habitual interest (in ball game, opera, etc.)
(Encyclopedia of Chinese Language, Shanghai Dictionary Press, 1999)

Yin: habitual craving, addiction (especially used for drugs).
(English-Chinese Medical Dictionary, Shanghai Science and Technology Press, 1984; reverse translation of the Chinese the definition of the entry "addiction" in English)

French

Dépendance/Toxicomanie: Terme générique recouvrant les notions de physicodépendence, de psychodépendance et de pharmacodépendance
Dictionnaire de médecine flammarion 1975

Generic term covering notions of physical dependence, psychological dependence and pharmacodependence.

German

Sucht/Suchtabhängigkeit: Mehr passives, zwanghaftes Angewiesensein auf die

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

Befriedigung eines Triebes ungeachtet des Verlustes an Selbstwert-u.
(Umweltbezug. Neben Nikotinabusus, Triebentartungen, chronischem Alkoholmissbrauch
Roche Lexikon Medizin 1984)

A rather passive, coercive dependence (in the sense of "to be left to one's own resources") on the satisfaction of a desire (in the sense of "urge", "drive", similar to sexual) ignoring the loss of relatedness to both oneself and to one's environment.
References made to: nicotine abuse, degeneration of desire (in the sense of "perversion"), chronic alcohol abuse.

Japanese

Shiheki: 1. One's special tendency to do one's certain favorite thing 2. (med.) sick condition when a person is always seeking stimuli such as alcohol and drugs, and has come to produce withdrawal symptoms.
(Sanseido, Encyclopedic Dictionary JIRIN21, Sanseido, 1993)

Tan-deki: Indulge in unhealthy amusements and disregard the other (e.g. be addicted to sensual pleasure).
Chu-doku: Induction of functional disturbance by taking harmful materials or inhaling toxic drugs etc. Usage: strong addictive narcotics; food poisoning
(Sanseido's New Japanese Dictionary, 1997)

Addiction: Shiheki (physical or psychological habitual dependence on a certain substances or conduct which is out of control)
(Stedman's Medical Dictionary 4th Ed., English-Japanese/Japanese-English, Tokyo, Medical Review, 1997)

C-2. Chronological changes in definitions in Webster's dictionary of English language

Webster's 1828 Dictionary
ADDIC'TION, n.
1. The act of devoting or giving up in practice; the state of being devoted.
His *addiction* was to courses vain.
2. Among the Romans, a making over goods to another by sale or legal sentence; also an assignment of debtors in service in their creditors.

Webster's 1913 Dictionary
Addiction
Ad*dic"tion (#), n. [Cf. L. addictio an adjudging.] The state of being addicted; devotion; inclination. His *addiction* was to courses vain." *Shakespeare*

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

Addict

[imp. & p. p. Addicted; p. pr. & vb. n. Addicting.] [L. addictus, p. p. of addicere to adjudge, devote; ad + dicere to say.]

To apply habitually; to devote; to habituate; -- with *to*. They *addict* themselves to the civil law." *Evelyn.* He is **addicted** to his study. *Beau. & Fl.* That part of mankind that **addict** their minds to speculations. *Adventurer.* His genius **addicted** him to the study of antiquity. *Fuller.* A man gross . . . and **addicted** to low company. *Macaulay.*

Webster's Third New International Dictionary of the English Language (1961)

Addiction

1. Obs, INCLINATION, BENT

2a. The quality or state of being addicted *specif:* the compulsive uncontrolled use of habit-forming drugs beyond the period of medical need or under conditions harmful to society (the extent of *addiction* ranged from 2 months to 10 years)

2b. Enthuastic devotion, strong inclination, or frequent indulgence (his *addiction* to comics) (his *addiction* to vivid metaphors)

3. [L addiction-, addictio, fr. addictus + -ion, -io –ion] : A formal award or assignment of a person or thing to another; *esp.*: an award made by a praetor or other magistrate (as of a debtor to a creditor)

Merriam-Webster Collegiate Dictionary 10th Edition

(http://www.britannica.com/bcom/dictionary/ ; June 22, 2000)

Ad·dic·tion

Pronunciation:	&-'dik-sh&n,	a-
Function:		*noun*
Date:		1599

1 : the quality or state of being addicted <*addiction* to reading>
2 : compulsive need for and use of a habit-forming substance (as heroin, nicotine, or alcohol) characterized by tolerance and by well-defined physiological symptoms upon withdrawal; *broadly* : persistent compulsive use of a substance known by the user to be harmful

C-3. The origin of the word addiction

(World Wide Words; an excerpt from http://www.quinion.com/words/index.htm):

"...To start with, in the sixteenth century, *addict* was an adjective, not a noun. It came from the Latin *addictus*, the past participle of *addicere*. In this the root *dicere* meant 'to say', but it also had a sense of 'adjudge' or 'allot', so that the whole word meant 'assigned by decree'. (*Dicere* is the root also of our *dictate* and *dictionary*, so that the phrase "addicted to dictionaries" might be thought an unnecessary repetition.) The English word *addict* to start with had the sense of being obligated or formally bound to someone else. Pretty soon, though, it took on a reflected meaning of being attached to something through one's own inclination, or of being devoted to some practice. Examples in the OED down to 1790 refer

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

to gluttony, lust, and "superstitious ceremonies".

The book *Coined by Shakespeare* says Shakespeare was the first recorded writer to use *addiction*, as a relatively neutral word with a sense something like "strong inclination"; in *Henry V*, the Archbishop of Canterbury could marvel at the king's knowledge of theology, since before then "his addiction was to courses vain", meaning he used to like activities of no value or importance. By the 1640s, it was being used in a similarly straightforward way to indicate that one was given to some habit or pursuit; as late as 1858, Gladstone could write about "Their addiction to agricultural pursuits" and this sense remains in use just as much today.

The adjectival form of *addict* is long defunct, but the word was pulled out of retirement at the beginning of the twentieth century as a noun for someone whose inclinations towards or devotion to a drug has led to dependence upon it. A new word was needed because it was only at this period that the medical condition was being recognised and concern was beginning to grow. Only a few years after it had been reinvented it began to be used again in the old sense in which *addiction* has for so long been employed, of someone who is merely devoted to some activity, especially a pastime or sport: the OED has an example from the *Westminster Gazette* of 1925: "Even many working men are night club addicts". It is this looser, colloquial usage that concerns the researchers, because they feel it has become more common in the past decade or so. They claim that as a result people are becoming confused about the distinction between addiction and some harmless hobby or activity taken a little too seriously.

The lexicographical evidence is against them. There seems no very strong evidence that usage of *addict* or *addiction* in what must now be called its figurative sense has changed much in the past decade. And it's clear from the evidence that the word has had this figurative meaning for centuries, and that it long predates the modern meaning which they take as its canonical one. The concern about drug addiction this century has biased our understanding of the word, but the sense they worry about has been there all along."

C-4. Description in Encyclopedia Britannica

drug use (http://www.britannica.com/bcom/eb/article/4/0,5716,118684+1,00.html)

"use of drugs for psychotropic rather than medical purposes. Among the most common psychotropic drugs are opiates (opium, morphine, heroin), hallucinogens (LSD, mescaline, psilocybin), barbiturates, cocaine, amphetamines, tranquilizers, and cannabis. Alcohol and tobacco are also sometimes classified as drugs. The term "drug abuse" is normally applied to excessive and addictive use of drugs. Because such drugs can have severe physiological and psychological, as well as social, effects, many governments regulate their use."

The nature of drug addiction and dependence

(http://www.britannica.com/bcom/eb/article/4/0,5716,118684+2+110090,00.html)

"If opium were the only drug of abuse, and the only kind of abuse were one of habitual, compulsive use, discussion of addiction might be a simple matter. But opium is not the only drug of abuse, and there are probably as many kinds of abuse as there are drugs to

Source: https://www.industrydocuments.ucsf.edu/docs/kfxk0001

abuse, or, indeed, as maybe there are persons who abuse. Various substances are used in so many different ways by so many different people for so many different purposes that no one view or one definition could possibly embrace all the medical, psychiatric, psychological, sociological, cultural, economic, religious, ethical, and legal considerations that have an important bearing on addiction. Prejudice and ignorance have led to the labelling of all use of nonsanctioned drugs as addiction and of all drugs, when misused, as narcotics. The continued practice of treating addiction as a single entity is dictated by custom and law, not by the facts of addiction.

The tradition of equating drug abuse with narcotic addiction originally had some basis in fact. Until recent times, questions of addiction centred on the misuse of opiates, the various concoctions prepared from powdered opium. Then various alkaloids of opium, such as morphine and heroin, were isolated and introduced into use. Being the more active principles of opium, their addictions were simply more severe. More recently, new drugs such as methadone and Demerol were synthesized but their effects were still sufficiently similar to those of opium and its derivatives to be included in the older concept of addiction. With the introduction of various barbiturates in the form of sedatives and sleeping pills, the homogeneity of addictions began to break down. Then came various tranquillizers, stimulants, new and old hallucinogens, and the various combinations of each. At this point, the unitary consideration of addiction became untenable. Legal attempts at control often forced the inclusion of some nonaddicting drugs into old, established categories--such as the practice of calling marijuana a narcotic. Problems also arose in attempting to broaden addiction to include habituation and, finally, drug dependence. Unitary conceptions cannot embrace the diverse and heterogeneous drugs currently in use.

Popular misconceptions

The bewilderment that the public manifests whenever a serious attempt is made to differentiate states of addiction or degrees of abuse probably stems from two all-too-common misconceptions concerning drug addiction. The first involves the stereotype that a drug user is a socially unacceptable criminal. The carry-over of this conception from olden times is easy to understand but not very easy to accept today. Ironically, the so-called dope fiend, if indeed one does exist, is likely to be a person who is not using an opiate. The depressant action of opium and its derivatives is simply not consistent with the stereotype. The second misconception involves the naïve belief that there is something magically druglike about a drug, which makes a drug a drug. Many substances are capable of acting on a biological system, and whether a particular substance comes to be considered a drug depends, in large measure, upon whether it is capable of eliciting a "druglike" effect that is valued by the user. There is nothing intrinsic to the substances themselves that sets one active substance apart from other active substances; its attribute as a drug is imparted to it by use. Caffeine, nicotine, and alcohol are clearly drugs, and the habitual, excessive use of coffee, tobacco, or an alcoholic drink is clearly drug dependence if not addiction. The same could be extended to cover

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tea, chocolates, or powdered sugar, if society wished to use and consider them that way. The task of defining addiction, then, is the task of being able to distinguish between opium and powdered sugar while at the same time being able to embrace the fact that both can be subject to abuse. This requires a frame of reference that recognizes that almost any substance can be considered a drug, that almost any drug is capable of abuse, that one kind of abuse may differ appreciably from another kind of abuse, and that the effect valued by the user will differ from one individual to the next for a particular drug, or from one drug to the next drug for a particular individual. This kind of reference would still leave unanswered various questions of availability, public sanction, and other considerations that lead people to value and abuse one kind of effect rather than another at a particular moment in history, but it does at least acknowledge that drug addiction is not a unitary condition."

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Appendix D. Evolution/history of PM position on the term addiction and how it relates to nicotine and/or smoking

Submission, 1994

- "There is no consensus within the scientific community regarding the definition of the term "addiction." As a result, the characterization of a behavior as an "addiction" turns on one's choice of a definition rather than verifiable scientific findings."

- "Under a traditional and scientifically verifiable definition of "addiction," a substance is "addictive" if it causes (1) intoxication, (2) physical dependence (as manifested by a well-defined withdrawal syndrome), and (3) tolerance."

- According to this definition of "addiction," neither cigarette smoking nor the nicotine delivered in cigarettes is "addictive."

- "The effects of nicotine neither fully explain smoking nor justify characterizing smoking as a form of "drug-seeking" behavior."

- "Empirical evidence establishes that many other factors are equally or more important motivators of smoking behavior."
  (Submission of Philip Morris USA and the American Tobacco Company to the Drug Abuse Advisory Committee in connection with its meeting on August 2, 1994, vol. 1.0 (July 29, 1994); citations from "Summary")

Before the United States Food and Drug Administration, 1996

- "Traditionally, the term "addiction" was reserved to describe the pharmacological phenomena of intoxication, tolerance, and a physical dependence that was manifested by withdrawal. Today, however, the concept of "addiction" is often indiscriminately applied to a seemingly endless arrant of products and activities."
- Thus, although some researchers now argue that many behaviors can properly be labeled as "addictions,"[17] others believe that only those involving the use of psychoactive substances should be considered as "addictions" or "dependencies."
- The chapter titles of this document include the following:
  - "Cigarette smokers are not "addicted" under the traditional scientific definition of the term"
  - "Self-administration studies do not establish that nicotine is similar to addictive drugs"
  - ""Drug discrimination" studies and "liking"/"subjective effects" studies do not establish that nicotine is similar to addictive drugs"
    (Comments of Brown & Williamson Tobacco Corporation, Liggett Group Inc., Lorillard Tobacco Company, Philip Morris Incorporated, R.J.Reynolds Tobacco Company, Tobacco Institute Inc., Volume III, Docket Nos. 95N-0253, 95N-0253J, April 19, 1996)

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Position statement, 1997

- "We recognize that nicotine, as found in cigarette smoke, has mild pharmacological effects, and that, under some definitions, cigarette smoking is "addictive." The word "addiction" has been and is currently used differently by different people in different contexts, and the definition of the term has undergone significant changes over the past several decades. In 1964, for example, the Advisory Committee to the Surgeon General of the United States concluded that smoking, although "habit forming," did not fit within its definition of "addiction." However, in 1988, the Surgeon General redefined the term, and concluded that smoking is "addictive." We have not embraced those definitions of "addiction" which do not include historically accepted and objective criteria, such as intoxication and physical withdrawal, as important markers."

- "We acknowledge that our views are at odds with those of the public health community, but in the last analysis there is little point to a continuing public debate about the definition of a word used both colloquially and technically to describe many different kinds of behavior. We continue to believe that people can quit smoking if they resolve to do so, but we recognize that it can be difficult to quit. Accordingly, to ensure that there is a single, consistent public health message on the issue of addiction, we will refrain from debating the issue other than as necessary to defend ourselves and our opinions in the courts and other forums in which we are required to do so..."
  (Industry submission to U.S. Senate Judiciary Committee, Philip Morris' Statement of Position, October 2, 1997)

PM website, 1999

"Cigarette smoking is addictive, as that term is most commonly used today."
(http://www.philipmorris.com)

Szymanczyk's testimony, Engle, et al., v. Philip Morris Inc., et al., June 13, 2000

"Q. Well, what's your definition of addiction?

A. Well, my definition of addiction is a repetitive behavior that some people find difficult to quit. Sometimes that's associated with a psychoactive drug, which is the case of nicotine in a cigarette, but people – some people are addicted to alcohol, but they quit drinking. They stop drinking alcohol.

And I don't – I don't think your definition of addiction, that you can't quit, makes any sense at all. I've never seen anybody who's concluded that that's what addiction means, that you can't quit."

"Q. Okay. That's how it's described.

And, of course, we're not talking about anything similar to heroin addiction or cocaine addiction; the common-day usage of addiction to you is like -- like coffee –

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A. Well, I didn't say that.

Q. -- rather than like heroin?

A. I wouldn't say that. I wouldn't put it in the camp of heroin, but I've never used heroin, so it would be hard for me to determine that.

But I said it's a – a repetitive behavior that some people find hard to quit, and it's associated with something that's psychoactive, and that's the case with nicotine."

Deposition of Parrish, Blue Cross and Blue Shield v. Philip Morris, June 14, 2000

"Q. The website uses the term, "Cigarette smoking is addictive as that term is most commonly used today." Do you know what is meant by the phrase, "as that term is most commonly used today"?

A. I believe it means that if someone continues to use a product or engage in an activity believing that it is harmful to you, and in the face of a desire to stop, that that activity or that substance is addictive. That's how I would explain it."

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Appendix E. What do we know about nicotine as it relates to smoking behavior?

Note: This is an on-going document as of July 2001.

1. Tolerance to nicotine

Animal studies

- Tolerance to the effect of nicotine in various species of animals is well established, since studies in the early 20th century (e.g. Dixon and Lee, 1912). It has been demonstrated that tolerance to the acute effects of nicotine e.g. for body temperature and rotarod performance, was associated with increases in the number of binding sites in various brain regions while the affinity was unaffected, showing the up-regulation of nicotinic receptor after chronic nicotine treatment (e.g. Marks et al., 1983).

- It is currently being studied which type of neuronal nicotinic receptors are upregulated, and how this relates to functional tolerance. For example, it has been reported that alpha and beta2 subunit mRNA levels in the brain did not change after chronic nicotine administration (e.g. Marks et al., 1992), while the elevation in alpha7 receptor subunit mRNA level has been reported in substantia nigra and ventral tegmental area but not in cortex and hippocampus (Ryan and Loiacono, 2001). The functional significance of these changes is yet to be determined.

Human studies

- It has been well recognized that "retrospective reports by smokers indicate that initial exposure to tobacco smoke produced dizziness, nausea, vomiting, headaches, and dysphoria, effects that disappear with continued smoking and are rarely reported by chronic smokers" (SGR88, pp. 45). However, not much has been studied systematically on development of tolerance to nicotine in humans.

- One such study reports that "Dose-effect curves were shifted to the right or dampened in smokers relative to nonsmokers for most subjective and some behavioral responses, consistent with chronic tolerance, but there was less evidence of chronic tolerance to other behavioral effects or to cardiovascular responses." Although the authors concludes that the pattern of chronic vs. acute tolerance appears similar, they also suggest that "different mechanisms may be responsible for these different effects of nicotine" (Perkins et al., 1994).

- Upregulation of nicotinic receptors has been reported in postmortem brain of smokers. Breese et al. (1997), reported that "a significant increase was seen in [3H]nicotine binding in both hippocampus and thalamus of subjects with life-long smoking histories...There was also a positive correlation between the degree of smoking, as measured by the average reported packs smoked per day, and the number of nicotine binding sites ..."

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2. Reinforcing effects of nicotine

Animal studies

- In an article entitled "The scientific case that nicotine is addictive", Stolerman (1995) described that:
  - "Solutions of pure nicotine can, in appropriate conditions, serve as a positive reinforcer in six different species (rats, rhesus monkeys, squirrel monkeys, baboons, dogs and humans)....In some experiments, rates of responding maintained by the reinforcing effect of nicotine approximate to those maintained by cocaine under the same condition..."
  - "In other studies, nicotine has shown only rather weak efficacy as a positive reinforcer, and some reports have been negative...These findings have led some people to conclude that nicotine has little efficacy as a reinforcer and that there must be other explanations for the use of tobacco products. It is difficult to maintain that non-drug factors do not play any role in tobacco use, but the positive reinforcing effect of nicotine cannot be discounted as being of primary and fundamental significance."
  - "The available information suggests that nicotine is a weaker reinforcer than some classical drugs such as cocaine....Thus, nicotine is powerfully efficacious under only a relatively narrow range of conditions and self-administration is often slow to develop...The weakness of the effects of nicotine relative to those of classical drugs is puzzling and the reasons are not understood."

- In the continuous intravenous self-administration experiment in rhesus monkeys, it has been reported that:
  - "The daily intake pattern was quite stable with relatively frequent intake during the lights-on period, and very low intake during lights off. The daily dose levels were also stable in each monkey, but varied among monkeys in the range of 200-2000 µg/kg. No tendency of gradual increase or decrease was observed in them. During active intake of nicotine, no manifestation of drug effects was observable, and the gross behavior remained as usual." (Yanagita et al., 1983).
  - "Progressive ratio test. The monkeys showed such high rates as 6400-12800 for the cocaine, and the rates paralleled unit dose. In contrast, no meaningful increase of the rate over saline was observable with the unit dose of nicotine 50 µg/kg. At 200 µg/kg, slightly higher rates, up to 1600, were obtained" (*ibid.*).
  - "The intensity of the intravenous drug-seeking behavior for nicotine observed in a progressive ratio experiment was found to be quite strong but weaker than that for morphine or cocaine. Pretreatment with frequent intravenous doses of nicotine for 4 weeks did not enhance the intensity. This result demonstrates marked difference between physical dependence on opiates such as morphine or codeine and on nicotine." (Yanagita et al., 1991).

- The above results in rhesus monkeys appear to be in line with an old observation on human smoking that "It is, moreover, common knowledge that the use of tobacco for smoking and chewing does not necessitate a progressive increase of the dose as in

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the case in other toxic substances.." (Lewin, 1931).

- Regarding the aversive effects of nicotine, it has been reported that "The response-produced i.v. injection of nicotine functioned effectively to suppress food-maintained responding by squirrel monkeys during the punishment component of a multiple schedule.", and that "In previous studies which demonstrated reinforcing effects of nicotine in squirrel monkeys [*ref. omitted*], nicotine injections were substituted for saline injections while responding was occurring at very low rates, each injection of nicotine occurred only after a relatively long sequence of responses and there was a specified minimum period of time between successive injections. Whether nicotine functions as a punisher to suppress behavior or as a reinforcer to maintain behavior may be influenced by such difference in the schedule of injection." (Goldberg and Spealman, 1983).

- The positively reinforcing and aversive effects have been observed at 10 μg/kg or more, with the highest response rate being observed at 30 μg/kg. Since both effects were not observed at 3 μg/kg, the threshold dose appear to be between 3 to 10 μg/kg (e.g. Goldberg et al., 1983).

Human studies

- In an intravenous self-administration of nicotine at 0.75-3 mg (1.5 mg injection was 18-22 μg/kg of body weights of the subjects), it has been reported that "Nicotine injections were taken in orderly patterns that were related in unit dose, whereas patterns of saline injections varied widely." (Henningfield et al., 1983). In this report the number of self-administration during the 3-hr session in 5 subjects ranged from 8 to 29 for nicotine 1.5 mg and that of saline appears to have ranged from 4 to 37.

- Intravenous nicotine at 0.75-3 mg reportedly increased scores of morphine-benzedrine group (MBG) scale, a measure of euphoria, as well as LSD-scale, a measure of dysphoria, of the Addiction Research Center Inventory (ARCI) in "linear functions of dose" (Henningfield et al., 1985).

- As in the animal studies, aversive effects of nicotine have also been observed in humans:
  - "Human volunteers were tested ....Nicotine was found to maintain responding that produced its injection under certain conditions, and to maintain responding that avoided its injection under other conditions." (Henningfield & Goldberg, 1983)
  - "Since nicotine can function either to maintain or suppress responding which produces its injection or to maintain responding that prevents its injection, it is not surprising that the precise effects of nicotine in the control of human smoking behavior have been difficult to determine. The nature of the control of smoking by nicotine is probably modified in response to changing environmental conditions." (Goldberg et al., 1983)

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3. Subjective effects of nicotine

Animal studies (drug discrimination)

- Since it has been shown that the internal states produced by nicotine can serve as discriminative stimuli (Morrison and Stephenson, 1969), the discriminative effects of nicotine have been extensively studied, mainly in rats.

- These studies in rodents have revealed that the discriminative effects of nicotine are pharmacologically specific in that the effects are substituted fully by centrally-acting nicotinic-cholinergic agents, nicotine analogues (e.g. anabasine) and metabolites (e.g. nornicotine) but not by other classes of compounds and that the effects are centrally mediated (for review see e.g. Stolerman, 1987). One exception for the former is that full substitution by amphetamine of nicotine-cue has been reported, and the author states that "... there is no obvious explanation for the discrepancy" (Stolerman, 1989).

- In squirrel monkeys no substitution by cocaine and morphine of nicotine has been observed (Takada et al., 1988). In rhesus monkeys trained to discriminate either nicotine or cocaine from saline (n=2 each); however, full substitution by cocaine of nicotine and by nicotine of cocaine was observed (n=2 each; Takada, unpublished observation). Further, full substitution by nicotine of cocaine been reported in "some monkeys" out of 3 trained to discriminate cocaine from saline (Garza and Johanson, 1983).

- Taken together, it appears that the discriminative effects of nicotine in animals differ at least to some extent from those of psychostimulants such as cocaine and amphetamines.

Human studies

- When volunteers with a history of drug abuse were given intravenous doses of nicotine, increases in the scores of the Addiction Research Center Inventory were observed on "MBG (or euphoria) and LSD (or dysphoria) scales" at 3 mg/kg, and "these increases were linear function of dose" (Henningfield et al., 1985). This report also states that "For these seven subjects, cocaine or amphetamine identifications were made on 86% of the tests at the 3.0-mg dose..."

- Studies utilizing non-smoking subjects without a history of drug abuse, however, have not shown such "euphoric" effects of pure nicotine given via nasal spray up to 20 µg/kg: "... nonsmokers tended to report decreases from base line in POMS*-vigor and arousal after the highest dose of nicotine." Difference in subjective effects of nasal nicotine noted between smokers and nonsmokers were: "smokers generally showed reduced responding to most subjective effects of nicotine, especially those which might be considered aversive (e.g. POMS-tension, VAS**-jittery)...smokers showed enhanced responding to more stimulating effects (POMS-vigor, POMS-arousal) of nicotine."

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* Profile of Mood Scale

** Visual Analogue Scale

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(Perkins et al., 1994).

- In a human drug discrimination study on nicotine (20 μg/kg via nasal spray), nicotine-appropriate responding in smokers was below 80% while that in never-smokers was nearly complete at the training dose. The authors argue that "...threshold for discrimination (i.e. lowest discriminable dose) may not differ between smokers and never-smokers" (Perkins et al., 1997).

4. Putative biochemical changes in the brain involved in nicotine reward

- Regarding the mechanism underlying drug reward, the stimulation of the mesolimbic dopaminergic system has been considered to play a crucial role. In rodents, nicotine has been reported to increase the extracellular level of dopamine in this brain region that is often interpreted as the evidence for the "addictiveness" of nicotine, since similar phenomena have been observed with prototypic drugs of abuse such as cocaine and morphine. Mesolimbic dopamine neurotransmission has been postulated to be modified by NMDAergic*** as well as GABAergic**** neurotransmissions. For example, ifenprodil, a relatively specific NR2B*** receptor antagonist has been reported to block rewarding effects of morphine (Narita et al., 2000). Nicotine is considered to increase the glutamate release in the ventral tegmental area (VTA), which induces stimulation of dopaminergic transmission in this area (e.g. Schilstrom et al., 1998). As for the involvement of GABAergic neurotransmission, it has been reported that intra-VTA injections of muscimol as well as baclofen suppressed intravenous self-administration of nicotine in rats (Corrigal et al., 2000). However, whether or not the similar change in midbrain dopaminergic system will be observed by nicotine in man and nonhuman primates is not clear (cf. page 12, Domino, 2000, personal communication). It is described in Cleminti et al., 2000, that "In conclusion, Domino remarked that very little is known about what goes on in the brains of tobacco smokers and more research on the role of NNRs in addiction is required."

- Taken together, it can be said that not much is known on the precise brain mechanism(s) underlying the reinforcing effects of nicotine.

5. Withdrawal signs after chronic nicotine treatment and smoking cessation

Animal studies

- In rodents, Malin and others have reported several studies, which describe withdrawal signs after cessation of continuous subcutaneous infusion of nicotine tartrate at 3-9 mg/rat/day. These signs include teeth-chattering/chews, writhes/gasps, ptosis, tremors/shakes, and yawns (e.g. Malin et al., 1992). These authors also reported that similar signs have been observed after the administration of mecamylamine as well as

*** NMDA: *N*-methyl-*D*-aspartate. Currently NMDA receptors are classified into NR1 and NR2 subtypes, with the latter being further classified into NR2A-D

**** GABA: gamma-aminobutyric acid

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naloxone during the chronic nicotine infusion (e.g. Malin et al., 1994). However, as for the nicotine withdrawal, as the authors described, "Surprisingly few animal models have been described, and these rely either on changes in conditioned behavioral responses [*ref. omitted*] or changes in body weight and food consumption [*ref. omitted*]." This observation as well as the reported withdrawal signs in rodents appear to indicate that the physical dependence potential of nicotine is weak.

- In rhesus monkeys, it has been reported that chronic nicotine treatment (hourly injection at 0.25 mg/kg, i.v. for 4 weeks) did not produce any appreciable changes in grossly observable behavior nor the increase in reinforcing efficacy of nicotine, as cited above (Yanagita et al., 1991). The effects of mecamylamine in these monkeys were not distinguishable from saline control (Takada, unpublished observation).

Human studies

- No data on chronic treatment of pure nicotine is available.

- The description of "withdrawal" can date back to 1931*. It is stated that "... the symptoms due to withdrawal of tobacco, if they occur at all, are easily overcome. The latter consist of an extreme feeling of discomfort and eventually bad humour and dejection. It is very exceptionally that graver symptoms occur" (Lewin, 1931).

- Diagnostic criteria for nicotine withdrawal in DSM-IV are:
  "Four (or more) of the following signs" followed within 24 hrs of abrupt cessation of nicotine use (smoking); 1) dysphoric or depressed mood, 2) insomnia, 3) irritability, frustration, or anger, 4) anxiety, 5) difficulty concentrating, 6) restlessness, 7) decreased heart rate, and 8) increased appetite or weight gain.

- Hughes and Hatsukami report that "we believe the valid signs and symptoms of tobacco withdrawal are craving for tobacco, irritability, anxiety, difficulty concentrating, restlessness, bradycardia, and increased eating". However, these authors also stated that "The clinical significance of tobacco withdrawal is also unknown." As a cause of tobacco withdrawal, "a simple behavioral reaction to the loss of a reinforcer" is listed in addition to the possibility of pharmacologic dependence (Hughes and Hatsukami, 1986).

- Many of the items of Fagerstrom Tolerance Questionnaire, which is widely used to measure the degree of "nicotine dependence", appear to relate to withdrawal. The items are: 1. How soon after you wake up do you smoke your first cigarette? (Answer: Within 30 min; After 30 min), 2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in cinema, etc.? (Y/N), 3. Which cigarette would you hate most to give up? (The first one in the morning; Any other), 4. How many cigarettes/day do you smoke? (15 or less; 16-25; 26 or more), 5. Do you

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* The anecdotal description of withdrawal is said to date back to 1527 (see "Tobacco Addiction References" http://medicolegal.tripod.com/tobaccoaddiction.htm)

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smoke more frequently during the first hours after awakening than during the rest of the day? (Y/N), 6. Do you smoke if you are so ill that you are in bed most of the day? (Y/N), 7. What is the nicotine level of your usual brand of cigarette? (0.9 mg or less; 1.0-1.2 mg; 1.3 mg or more), 8. Do you inhale? (Never; Sometimes; Always). (Fagerstrom and Schneider, 1989)

5. Sensory aspects

- Both cigarette smoking and peripheral administration of nicotine stimulates the sensory branches of five of the twelve cranial nerves (e.g. Warwocl and Williams, 1973):
  - In the mouth, smoking and nicotine stimulate the chorda tympani, glossopharyngeal and trigeminal nerves.
  - In the throat, smoking and nicotine stimulates the glossopharyngeal and vagus nerves.
  - In the nose, smoking and nicotine stimulates the olfactory and trigeminal nerves.

- The taste properties of nicotine have been reported for well over 100 years ago (Grey and Richet, 1885). It has been reported that nicotine produces a bitter taste at low concentrations while evoking a burning sensation at high concentrations which can be blocked by nicotinic antagonist mecamylamine (Dessirier et al., 1997; Jarvik and Assil, 1988). Specific nicotinic receptors have been identified on the tongue and in the throat in rats (Liu et al., 1993) and some of these receptors have also been reported to respond to capsaicin (Lui and Simon, 1996). To what extent this "taste" property of nicotine is contributing to smoking behavior is largely unknown.

- It is well known that nicotine takes on the odor of tobacco when exposed to air, and the smell of nicotine changes its quality as concentration increases: at medium concentration burning smell is generated in addition to tobacco odor and at high concentration "stinging" odor is added (Thueraurf et al., 1999). It has been reported that "craving" for cigarettes was lessened when smokers were given a nebulizer delivering citric acid in a fine mist (Rose and Hickman, 1987). Thus it appears that sensory stimulation, to some extent regardless of the quality of the odor, would play an important role in smoking behavior. That partial blockade of upper and lower airway sensation by the topical application of lidocaine resulted in "a significant linear decline in cigarette craving" would support this notion (Rose et al., 1984). These researchers, using denicotinized cigarettes, concluded that "many of the positive subjective effects from a denicotinized cigarette were comparable to that of a standard cigarette" and that "these data support the hypothesis that replacement of the sensory cues of smoking with 'airway sensory replacement' may be useful for smoking cessation" (Westman et al., 1996).

- In addition to nicotine and smoke's well-known pharmacological properties, it should be obvious from the above that nicotine and smoke have diverse sensory properties. The relative contributions of pharmacology and sensory physiology to the enjoyment of

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smoking is currently unknown. An experiment would need to be conducted where a centrally inactive sensory substitute for nicotine was used. Unfortunately, at present such a substitute does not exist.

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Appendix F. Disease criteria (ICD-10* and DSM-IV**)

Table. Criteria for "Dependence syndrome" in ICD-10 and "Substance dependence" in DSM-IV are shown.

ICD-10	DSM-IV
Dependence syndrome: characterized as a cluster of effects after repeated use of a substance resulting in three or more of the following symptoms:	Substance Dependence: A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period
1. a strong desire or sense of compulsion to take the substance	(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use
2. an impaired capacity to control substance-taking behavior in terms of its onset, termination, or levels of use; substance use with the intention of relieving withdrawal symptoms and with awareness that this strategy is effective	(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance(e.g., chain-smoking), or recover from its effects
3. a physiological withdrawal state	(1) withdrawal, as manifested by either of the following: (a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for Withdrawal form the specific substances) (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
4. evidence of tolerance such that the increased doses of the substance are required in order to achieve effects originally produced by lower doses	(2) tolerance, as defined by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of the substance (3) the substance is often taken in larger amounts or over a longer period than was intended
5. Progressive neglect of alternative pleasures or interests in favor of the substance	(6) important social, occupational, or recreational activities are given up or reduced because of substance use
6. Persisting with substance use despite clear evidence of overtly harmful consequences	(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

* World Health Organization, *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines* (1992)

** American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Washington, D.C.: American Psychiatric Association (1994)

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"Nicotine Dependence" is characterized as follows in the DSM-IV:

- Nicotine Dependence
  "...Some of the generic Dependence criteria do not appear to apply to nicotine, whereas others require further explanation... Many individuals who use nicotine take nicotine to relieve or to avoid withdrawal symptoms when they wake up in the morning or after being in a situation were use is restricted.... Individuals who smoke and other individuals who use nicotine are likely to find that they use up their supply of cigarettes or other nicotine-containing products faster than originally intended.."

- Nicotine-Induced Disorder
  292.0 Nicotine Withdrawal
  "These symptoms are in large part due to nicotine deprivation... The more rapid onset of nicotine effects with cigarette smoking leads to a more intensive habit pattern that is more difficult to give up... Mild symptoms of withdrawal may occur after switching to low-tar/nicotine cigarettes..."

- Among various compounds, characteristics of nicotine in relation to "substance dependence" is summarized in the following table in DSM-IV (modified by Takada – see the note in the Table).

DSM-Ⅳ, APA 1994

Table 1. Diagnoses associated with class of substances1)

	#Category	Depen-dence	Abuse	Intoxi-cation	With-drawal	Intoxi-cation Delirium	With-drawal Delirium	Dementia	Amnestic Disorder	Psychotic Disorders	Mood Disorder	Anxiety Disorders	Sexual Dysfunc-tions	Sleep Disorders
Polysubstance	1	X												
Nicotine	2	X			X									
Caffeine	3			X								I		I
Cannabis	6	X	X	X		I				I		I		
Hallucinogens	7	X	X	X		I				I*	I	I		
Phencyclidine	7	X	X	X		I				I	I	I		
Inhalants	8	X	X	X		I		P		I	I	I		
Opioids	9	X	X	X		I				I	I		I	I/W
Amphetamines	10	X	X	X	X	I				I	I/W	I	I	I/W
Cocaine	10	X	X	X	X	I				I	I/W	I/W	I	I/W
Alcohol	13	X	X	X	X	I	W	P	P	I/W	I/W	I/W	I	I/W
Sedatives, hypnotics, or anxiolytics	13	X	X	X	X	I	W	P	P	I/W	I/W	W	I	I/W
Other	13	X	X	X	X	I	W	P	P	I/W	I/W	I/W	I	I/W

* Also Hallucinogen Persisting Perception Disorder (Flashbacks)
Note: X,I,W,I/W, or P indicates that the category is recognized in DSM-IV. In addition, / indicates that the specifier With Onset During Intoxication may be noted for the category(except for Intoxication Delirium); *W* indicates that the specifier With Onset During Withdrawal may be noted for the category (except for Withdrawal Delirium); and *I/W* indicates that either With Onset During Intoxication or With Onset During Withdrawal may be noted for the category. P indicates that the disorder is Persisting.

1) The order of listing was modified by Takada
#Category:Number of categories recognized in DSM-Ⅳ shown in the table; added by Takada to the orignal list.

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Appendix G*. Chronological Events: World Health Organization, U.S. Public Health Authorities and Nicotine Pharmacology

Year	World Health Organization	U.S. Public Health Authorities	Nicotine Pharmacology	Notes
1905			Nicotinic receptors	Langley, "receptive substances of the cells"
1912			Tolerance	Dixon and Lee: tolerance to nicotine in rabbits
1931			Withdrawal	Lewin, "symptoms due to withdrawal of tobacco"
1942			Nicotine replacement	Johnston and Glasg, i.v./s.c. nicotine effects in humans
1957	Expert Committee: Clarification on "addiction" and "habituation"			
1958			Susceptibility	Fisher, twin study on smoking
1964	Expert Committee: "Dependence" to replace "addiction" and "habituation"	SGR: adopted WHO's 1957 definition of "addiction" and "habituation"		
1967			Reinforcing effects	Deneau and Inoki, i.v. self-administration, rhesus
1968			Pharmacokinetics	Armitage et al., smokers, cats and rats, "Pharmacological basis for the tobacco smoking habit"
1969			Discriminative stimulus	Morrison and Stephenson, rats
1970			Nicotine titration theory	Ashton and Watson, ".. Smokers automatically adjust the nicotine dose.."
1973			Nicotine antagonists on	Stolerman et al., mecamylamine, smokers
			Nicotine gum	Ferno et al., "a substitute for tobacco smoking"
1978			"Bolus effect"	Russell, smoking as "a dependence on high-nicotine
			Dopamine hypothesis	Wise, "it may be that DA plays an interesting and critical
1981			Reinforcing effects	Goldberg et al., "robust" self-administration of nicotine, squirrel monkeys
1984			Non-nicotine pharmacology	Glassman et al., effects of clonidine
			Withdrawal	Hatsukami et al., "It remains to be determined ...."; Hughes et al., "tobacco withdrawal syndrome is caused, in part, by nicotine deprivation"
1988		SGR: "the term "drug addiction" and "drug dependence" are scientifically equivalent"		
1992	ICD-10: "Dependence syndrome"			
1994				DSM-IV, "Substance dependence"
2001		IOM: "nicotine is addictive"		

*For references see Appendix H

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